# AMERICAN SECTION.

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## PRESENT CONCEPTS OF TUBERCULOUS INFECTION AND DISEASE: CLINICAL AND PATHOLOGICAL CONSIDERATIONS.[1]

### ACQUIRED AND CONSTITUTIONAL FACTORS IN RESISTANCE TO TUBERCULOSIS.

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THERE is almost universal agreement to-day on a distinction between first infection and reinfection types of tuberculosis. In contrast to old views, it is now generally agreed that the first infection type of tuberculosis is usually benign. One school of thought to-day considers it serious, chiefly on the ground that it paves the way, physiologically and immunologically, for the destructive reinfection type of tuberculosis. That it has this effect is generally admitted, but it must be conceded, on the other side, that it is not the sole pre-requisite for the ulcerative form, since age and other factors enter. At the same time, there is sound reason to believe that first infection sets in motion forces in the opposite direction. An abundance of experimental investigation in animals has established the immunising character of first infections of mild type or moderate extent.

While we must admit that the reinfection type of tuberculosis can occur only in the presence of a pre-existing primary infection, we have reason to believe that in a large number of people the primary infection confers an immunity that prevents subsequent infection altogether or keeps it from becoming progressive. The finding at post-mortem examination of the combination of healed childhood type tuberculosis and healed adult type tuberculosis (in the form of apical scars) is more common than the finding of healed childhood type tuberculosis combined with progressive disease of the adult type.

In regions of widespread infection, the great majority of adults may exhibit evidence at post-mortem examination of both childhood and reinfection types of infection (90 per cent. or more, Aschoff). Most of the reinfection lesions are simply small healed lesions at the apex. It would be unwarranted to say without qualification that the childhood type disease furnished an immunity which prevented the adult type disease from becoming progressive in cases of the latter group, because we have no means of measuring immunity to tuberculosis, but animal experiments at least suggest that this might be the case.

Such differences as occur in the extent of adult type tuberculosis must be evaluated in the light of the size of the reinfecting dose, a matter on which our knowledge, however, can never be exact. We may attempt to estimate the dosage of infection on a comparative basis. The length of time of exposure can usually be determined. And a tuberculosis patient

[1] Joint Symposium, Thirty-first Annual Meeting of N.T.A., Saranac Lake, New York, June 27, 1935.

with progressive excavating disease of the lungs, and careless about cough and disposal of sputum, presumably transmits larger infecting doses of tubercle bacilli to those about him than a patient with less advanced disease who is careful in his hygienic behaviour. But as to the actual quantitative relationships involved we have no knowledge.

Equally important for consideration and further study is the age factor. The relative immunity to reinfection-tuberculosis in children up to the years of adolescence, children who have obvious childhood type tuberculosis and are known to be repeatedly exposed to tubercle bacilli, is still to be explained. In the mortality curves, and also in curves based on the incidence of clinically recognisable tuberculosis, there is a long trough between the years of infancy and early childhood on the one hand, and the period of adolescence on the other. This trough covers a decade, and during the period so represented tuberculosis is relatively uncommon (particularly in the white race) as a cause of either illness or death. The peaks on either side of the trough in the mortality curve correspond to quite different types of tuberculosis. The one in the early years represents death from progressive forms of the childhood type disease, while the rise and peak after adolescence are the result of the familiar, excavating and destructive adult-type (reinfection-type) disease.

The relative immunity to reinfection type tuberculosis in children up to the years of adolescence is still to be explained. Their freedom from progressive disease cannot be attributed to lack of infection. In countless families the same exposure that resulted in the childhood type disease continues after the latter heals, without visible evidence of new infection. With adolescence, however, there is a startling reappearance of tuberculous lesions in the exposed children, this time of the adult type.

Why has the "adult" form been so long in manifesting itself? Is a protective factor in operation during the decade of relative immunity, or has the physiological process of sexual maturation introduced a specific element of susceptibility? These are questions for which we have no answer. Whatever has happened, the effect is manifested in an increased capacity of the cause of the disease to progress within the host. The type of the disease is indeed changed, but the variation is not the result of the increased age of the host. Evidence in abundance is at hand that the change in type is an immunological effect, representing the new development of disease in tissues modified in responsive capacity by previous infection. Moreover, when first infections are acquired in adult years, an event of increasing frequency under modern conditions, they have the character of first infections in childhood.[1] Moreover, again, under conditions of repeated massive exposure, childen as young as 8 years of age may develop characteristic adult type tuberculosis. But in general, in the presence of repeated tuberculous infection, the decade preceding adolescence is one of relative freedom from the reinfection type of disease, and the reason for this fact is still to be learned.

[1] See Terplan (*Amer. Rev. Tuberc.*, 1934, 29, 77). However, Sweany has submitted some evidence to the contrary (*Amer. Rev. Tuberc.*, 1933, 27, 575), describing what appeared to be first infections in adult years, which exhibited certain anatomic features characteristic of the "adult type."

Coupled with the age factor sex plays an important part in susceptibility to reinfection- or adult-type tuberculosis. While the sexes seem on a par in resistance in the decade preceding adolescence, a difference is apparent immediately afterward. Girls mature first, and likewise manifest susceptibility to the reinfection type of tuberculosis before boys. This is seen not only in the mortality curves, but in the larger number of female cases seen clinically in the teen ages.

The factors making for all the variability in resistance as modified by sex and age may be grouped under the terms "inherent" or "constitutional." The terms are applied to indicate a difference from conditions set up by the chance acquisition of immunising, or at least "resistance-modifying," previous infections. That inherent constitutional factors play an important part in resistance and susceptibility to tuberculosis is readily proved by animal experimentation.

It is well known that animals in nature vary widely in their susceptibility to the disease, and the variation is readily demonstrated quantitatively in the laboratory. Indeed, minute but important differences in tissue response to the same quantity of the same strain of tubercle bacilli in different animals can be studied under the microscope, and the differences noted yield important information for the whole theory of constitutional susceptibility. If minute doses of human type tubercle bacilli of comparable size are introduced into guinea-pigs and cats, for example, a ready growth of the micro-organism will be noted in the one and a failure of growth in the other. The failure in the cat is not the result of a rapid, destructive action on the part of the cat's fighting cells. The explanation lies deeper; it is either that the cat's fluid juices inhibit the organism in ways beyond our power to detect, or that the bacilli fail to find the proper nutritive conditions in that particular environment. In the guinea-pig, on the other hand, there is at the same time an acute inflammatory outpouring of cells and, in spite of it, a progressive multiplication of the bacilli introduced.

These are wide differences, easily seen and generally admitted. The objection may be made that nothing comparable to such differences can be seen within a single species and in particular within the single species, man.

However, significant, if less marked, differences can be shown experimentally in a single animal species. Some years ago Paul Lewis and Sewall Wright carried on an investigation illustrating wide, hereditarily transmissible variation in the resistance of different stocks of guinea-pigs to tuberculosis. At the present time Lurie, in the Phipps Institute, is in possession of inbred stocks of rabbits displaying a considerable range of variation in innate resistance or susceptibility to tuberculosis. With a dozen highly inbred families of different racial ancestry, exposed to inhalation infection in cages, he is able to distinguish stocks of three types, displaying respectively relatively low, intermediate and high resistance to tuberculosis. Families in the first group contract the disease soon after exposure, and die shortly of generalised tuberculosis. In marked contrast those in the third group, well exemplified in one family of English ancestry, are slow to acquire the disease, resist infection for a long period and finally die with disease of a very chronic type. Families in the second group are

intermediate in both respects. The reasons for the variation are not yet perfectly clear, but clues of importance are constantly coming to light.

It is only reasonable to attempt the explanation of human variability to tuberculosis in the light of such experimental observations. Here, admittedly, we enter one of the most strongly contested fields of epidemiology. At once the difference between white and Negro tuberculosis comes to mind, and at once we encounter the difficulties set by multiplicity of uncontrolled factors. Negroes and whites are not only different racially, but in general, because of social and economic conditions, live differently, and hence such differences in susceptibility to tuberculosis as are apparent may be variously explained, on such grounds as crowding, massive or continued infection, inconstant nutritive state, and so forth, as well as inherent constitutional difference. I would not, for one minute, minimise the environmental factors, and the situation is so complex that it would be futile to attempt an analysis in the brief time here afforded.

On the other hand, one cannot refrain from speculating on certain facts of racial variability. Apparently, as time goes by, the range of variation in racial resistance in man is narrowing. The tuberculosis of Negroes, Polynesians, Eskimos and other groups with former astounding tuberculosis mortality, appears to be far less acute, in general, in its anatomical type to-day. Have improved living conditions, with better environment and less opportunity for massive infection, been responsible, or has there been an elimination of the most susceptible stocks by the disease, with natural selection of the more resistant strains for survival?

Obviously animal experimentation affords better opportunity for study of racial factors than do human conditions. Environmental factors can be controlled. However, once in a while a human experience is recorded that has some of the value of a laboratory experiment. In the present connection an event significant for human epidemiology, well described by Ferguson,[1] may be recalled.

In brief this event, which may be likened to a laboratory experiment, was as follows. About 1880, due to the extermination of the buffalo, the Indians of the Canadian plains entered the Reservations, leaving the open conditions of the prairie for close-set permanent homes and conditions of continual crowding. Tuberculosis soon appeared and rapidly reached epidemic proportions. By 1884 the mortality was high and in 1886 reached an astounding figure in certain reservations. For the Qu'Appelle Valley reasonably reliable vital statistics gave a rate of 9,000 per 100,000 living.

This seems too high a figure, as compared with any known rates for whites, to attribute to environmental conditions alone. The Indians had had little previous experience with tuberculosis and it is reasonable to believe that little of Nature's process of survival of the fittest, as far as tuberculosis was concerned, had been brought to bear upon them. However, the initiating rôle of environment in the high mortality must be admitted.

But the sequel is significant. Within less than a decade a great drop

[1] *Trans. 14th Ann. Conf. of the Nat. Assn. Prevention Tuberc.* (Eng.), 1928; *Trans. 29th Ann. Meeting Nat. Tuberc. Assn.*, 1933, 93.

in the recorded annual mortality took place, after which a much slower decline followed. It is difficult to believe that an effective improvement in environmental factors could have occurred quickly enough to cause the initial drop. In the absence of a complete set of pertinent facts it is just as reasonable to believe that the unselected Indians included a certain percentage of highly susceptible stock rapidly eliminated by the adverse conditions. Indeed specific analysis of the records with respect to family resistance to tuberculosis brought to light a definite variation, coupled with variation in resistance to other diseases, so that survival was assured to families resistant to the white man's diseases in general. A few families apparently naturally resistant to tuberculosis, and a few that were susceptible to the point of extermination, were discovered. In the succeeding generations the mortality rate had become far lower than the rates of the eighties and early nineties, but, obviously, a known improvement of living conditions may be as much responsible for the improved mortality rate as the elimination of susceptible parent stock.

Such accidental experiments have occurred repeatedly, and from the records obtainable—from Indians, Negroes, South Sea Islanders, Eskimos and others—many of us have formed the opinion that in all human history, in all races in contact with the tubercle bacillus, an adjustment between man and the bacillus has come about, with elimination, more or less rapid, of the more susceptible stock. The white race has advanced the farthest in this respect ; yet it, too, retains some elements more susceptible than others, and to this fact may be attributed a certain amount of the variation we see in the response of white people to infection. Again I would say that the well known environmental factors of crowding, intensity of exposure, nutrition, and other factors of strain in living, are equally or probably more responsible for such variation in white susceptibility as we see. I am only calling attention to factors less stressed in recent years than environment, and not emphasised by other speakers in this symposium, namely constitution and heredity.

Obviously our present programme of reduction in the spread of infection is in direct opposite direction to the drastic operation of the law of survival of the most fit. From the practical standpoint, however, there is little argument against our present campaign of limiting all infection in so far as possible. Unquestionably this tends to postpone primary infections to adult years, but anatomical evidence indicates that late primary infections, like early ones, usually run a benign course. And if, in the long run, it must be admitted that our campaign preserves physiologically susceptible stock, steadily wiped out by the disease in former eras, presumably the advance of knowledge will enable us to deal with this fact in the future.